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Gene Section

Review

NDC80 (NDC80, kinetochore complex component)

Manuela Ferrara, Francesca Degrassi

Institute of Molecular Biology and Pathology, Italian National Research Council, c/o Sapienza University, via degli Apuli 4, 00185 Rome, Italy francesca.degrassi@uniroma1.it

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Abstract

Review on NDC80, and where the gene is implicated.

Keywords
NDC80, Hec1, kinetochore complex, kinetochore-microtubule attachment

Identity

Other names
HEC, HEC1, TID3, KNTC2, HsHec1, hsNDC80, commonly known as Hec1 in humans.

HGNC (Hugo)
NDC80

Location
18p11.32

DNA/RNA

Description

The human NDC80 gene lies on the p arm of chromosome 18, close to the telomeric region; Position 2,571,511 to 2,616,635, forward strand (Ensembl ID: ENSG00000080986).

Transcription

The full mRNA comprises 2172 bp (Ensembl ID: ENST00000261597.8). The transcript contains 17 exons. Ensembl reports the existence of 5 splice variants. Analysis of the 5'-flanking region showed that it contains binding sites for cAMP responsiveelement binding (CREB) and activating transcription factor 4 (ATFA or CREB 2) proteins that positively regulate transcription (Cheng et al, 2007).

Pseudogene

No pseudogenes are described in humans.

Protein

Description

642 aa; 73.9 kDa.
"Highly Expressed in Cancer protein 1" (Hec1) is the name of the human homologue of the Ndc80 protein. It was originally identified as an interactor of the retinoblastoma (pRb) protein in the yeast two-hybrid system (Chen et al, 1997). It was subsequently re-isolated as an interactor of the mitotic checkpoint protein MAD1L1 (Martin-Lluesma et al, 2002).
Hec1 interacts with three other kinetochore proteins (NUF2, SPC25 and SPC24) to form the Ndc80 kinetochore complex that is required for establishing stable interactions between the kinetochore and microtubules (Ciferri et al, 2005; DeLuca et al, 2006; DeLuca & Musacchio, 2012). The complex has an elongated rod-like structure that spans ~60 nm, with globular domains at both ends. The globular domains of Nuf2 and Hec1 interact with the microtubules at

one end whereas the Spc24-Spc25 globular heads constitute the centromere binding domain of the complex

The crystal structure of a truncated version of the Ndc80 complex has been resolved and different Hec1 structural domains have been identified (Ciferri et al, 2008). The N-terminus comprises an unstructured tail domain (aa 1-80) which is highly basic and positively charged. The Hec1 tail is required for the efficient formation of stable kinetochore-microtubule attachments in mammalian cultured cells (Guimaraes et al, 2008; Miller et al, 2008) and the affinity for microtubules of the entire complex is modulated by AURKB (Aurora B)-mediated phosphorylation on Ser8, Ser44, Ser15, Ser55 residues within the tail domain

A second portion of the N terminus folds into a Calponin Homology (CH) domain (aa 81-196), a motif found in actin- and microtubule-binding proteins. The CH domain contributes to microtubule binding and attachment stability through a direct interaction between a positively charged regionin the CH domain and a negative region at the alpha and beta tubulin interface on microtubules (Alushin et al, 2010). Within the CH domain, Ser165 is phosphorylated by the mitotic NEK2 (NEK2A) kinase and expression of a non -phosphorylatable Hec1 has been shown to perturb chromosome congression and increase the number of erroneous kinetochore-microtubule interactions (Du et al, 2008).

The long coiled-coil region (aa 261-445) interacts with a similar region of Nuf2 producing the elongated rod-like structure. This domain is interrupted by a loop region in Ndc80 (aa 426-459), forming a kink in the Ndc80 complex structure. This region is required to establish end-on microtubule attachments to kinetochores through the binding of the spindle and kinetochore associated (Ska) complex and the Ctd1 replication licensing factor (Wan et al, 2009; Zhang et al, 2012; Varma et al, 2012). Finally, the C terminus (446-642) takes part in a tetramerization domain where the Ndc80/Nuf2and Spc24/Spc25 dimers interact (Ciferri et al, 2005).

Expression

The protein is present in actively proliferating tissues such as testis, spleen and thymus in mice (Chen et al, 1997). Hec1 expression is cell cycle regulated. In both untransformed and cultured cancer cells, the protein appears in late S and remains at high levels until mitosis, when it is down-regulated through anaphase promoting complex/cyclosome-Cdh1 (APC/C-Cdh1) and proteasome-mediated degradation (Li et al, 2011; Ferretti et al, 2010).

Localisation

Hec1 is a mitotic kinetochore protein. It localizes to nuclei in S phase and G2 cells. At the beginning of mitosis the protein localizes to the outer layer of the kinetochore (Wan et al, 2009), where it persists until it is degraded at the end of mitosis (Figure 1).

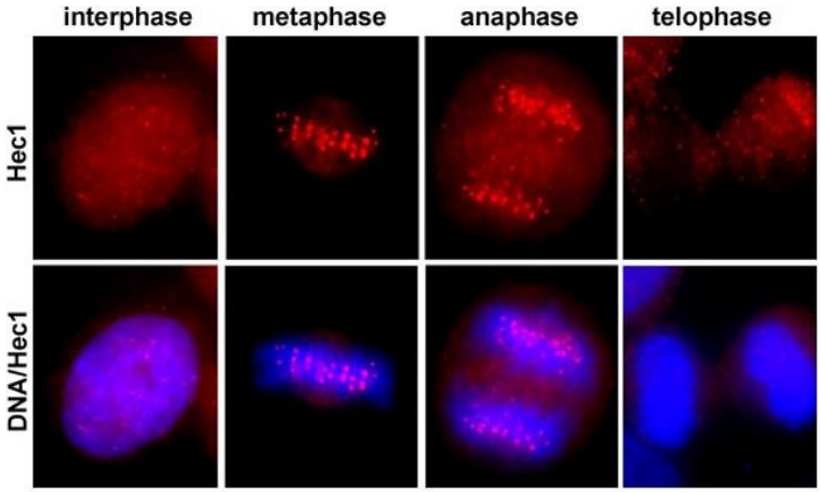

Fig 1. Hec1 localization in human cells. Immunofluorescence images of HeLa cells stained with DAPI (blue) and anti-Hec1 antibody (red). Hec1 is nuclear in interphase G2 cells, localizes to kinetochores at all mitotic stages and is degraded from kinetochores at telophase.

Function

Kinetochore-microtubule interactions:

Faithful chromosome segregation occurs when the two sister kinetochores are connected to microtubules emanating from different spindle poles (amphitelic attachment). However, in the early stages of mitosis non functional kinetochore-microtubule interactions (syntelic and merotelic attachments) intervene and must be corrected before anaphase to impede chromosome mis-segregation

and aneuploidy (Cimini & Degrassi, 2005). Hec1 is a constituent of the evolutionary conserved Ndc80/Hec1 complex that mediates the attachment of sister chromatids to the mitotic spindle and is therefore implicated in producing amphitelic end-on attachments and directing chromosome movements during mitosis (Tooley & Stukenberg, 2011). Molecular affinity beetween Hec1 and microtubules is mediated by electrostatic interactions involving positively charged amino acid residues on the Hec1 tail and CH domain that interact with negatively charged residues on microtubules (Ciferri et al, 2008; Sundin et al, 2011; Tooley et al, 2011). Consequently, the temporally regulated phosphorylation of Hec1 N terminal tail by Aurora B kinase during prometaphase decrease the affinity of the Ndc80 complex to microtubules, allowing the detachment of erroneous kinetochore-microtubule interactions and enabling the formation of new correct attachments (Zaytsev et al, 2014; DeLuca et al, 2011). Phosphorylation by NEK2A kinase of the CH domain also contributes to this process. Finally, kinetochore-microtubule attachments are stabilized by the recruitment of the Ska complex and Cdt1 at the Ndc80 internal loop to form functional end-on attachments (Zhang et al, 2012; Varma et al, 2012).

Mitotic checkpoint signaling:

Several pieces of evidence indicate that Hec1 plays a positive role in the spindle assembly checkpoint (SAC). This conserved cellular mechanism inhibits anaphase onset until all kinetochores are amphitelically attached to the microtubules and inter-kinetochore tension is present. Unattached kinetochores recruit SAC components that are then released from kinetochores to inhibit the anaphase promoting complex/cyclosome necessary for sister chromatid separation and mitotic exit (Musacchio, 2015). The Ndc80 complex is a structural component of the kinetochore and is required for proper SAC control as it recruits the ZW10 complex (Lin et al, 2006; Kops et al, 2005) that is essential for the binding of the master checkpoint proteins MAD1L1 and MAD2L1 to kinetochore (Martin-Lluesma et al, 2002; DeLuca et al, 2003). Furthermore, Hec1 has been shown to specify the kinetochore localization of the checkpoint kinase TTK (Mps1) via its microtubule binding domain (Stucke et al, 2004; Zhu et al, 2013). Hec1 phosphorylation by Aurora B kinase weakens the kinetochore-microtubule interaction but promotes Hec1 binding to Mps1, suggesting a concerted regulation between kinetochore attachment and checkpoint signaling (Zhu et al, 2013; Hiruma et al, 2015). Significantly, recent work has shown that formation of stable kinetochore- microtubule attachments, irrespective of inter-kinetochore tension, is sufficient to satisfy the SAC in human cells (Tauchman et al, 2015)

Implicated in

Various Cancer

Ndc80/Hec1 is a constituent of the NDC80 complex. The complex is required for accurate chromosome segregation in mitosis, as it is essential for generating bipolar end-on kinetochore-microtubule attachments, which are responsible for the faithful anaphase segregation of sister chromatids (DeLuca & Musacchio, 2012). Chromosome mis-segregation results in genome instability, which is a hallmark of cancer. The crucial role of the NDC80 complex in chromosome segregation during mitosis, the recurrent HEC1 upregulation in different human cancers (as described in sections below) and its dependence on pRb deficiency (Ferretti et al, 2010) suggest that Hec1 deregulation may be an important step in the multistage process of tumorigenesis. Concordantly, Hec1 depletion by RNa interference (RNAi) leads to defective mitotic checkpoint signaling, defective chromosome alignment to the metaphase plate and massive chromosome mis-segregation and apoptosis (Martin-Lluesma et al, 2002; Kaneko et al, 2009; Mattiuzzo et al, 2011; Linton et al, 2014; Ju et al, 2017). Interestingly, Hec1 overexpression in an inducible mouse model has been shown to promote chromosome instability in embryonic fibroblasts and tumor formation in different mouse tissues (Diaz-Rodriguez et al, 2008). Moreover, NDC80 is one of the genes defining a 11 gene signature associated with poor prognosis in multiple cancer types (Glinsky et al, 2005). This signature identifies a metastasis-enabling, anoikis-resistant, aneuploid-prone phenotype (Glinsky, 2006).

Breast Cancer

A real-time reverse transcription polymerase chain reaction (RT-PCR) study investigated expression of 76 mitotic spindle checkpoint genes in a large panel of breast tumor samples (including normal breast tissues, benign breast tumors, ductal carcinoma in situ, and grade I and III invasive ductal breast tumors). The study identified NDC80/Hec1 as one of the genes markedly upregulated in ductal grade III breast tumors. More interestingly, Ndc80 was specifically involved in the transition from normal breast tissues to benign breast tumors. Indeed, it was found as the most strongly upregulated gene in benign breast tumors, being its levels > 3-fold higher in begnin tumors than in normal breast tissues (Bièche et al, 2011). Moreover, NDC80 is part of several multigene expression profiles, which are commonly used in clinical settings to characterize breast cancer tissues for individualization of therapy (Koleck Conley, 2016).

A study on the relationships between host single-nucleotide polymorphisms (SNPs) and pretreatment cognitive performance in post-menopausal women diagnosed with early stage breast cancer has identified Ndc80 as one of 22 genes with a positive

association between host polymorphisms and improvement in cognitive function performance (Koleck et al, 2017).

Pancreatic Cancer

NDC80 mRNA and protein have been found overexpressed in pancreatic cancer tissues and in pancreatic cancer cell lines (Meng et al, 2015). Immunohistochemical evaluation of human pancreatic cancer tissues suggested that Ndc80 overexpression is significantly associated with clinicopathological parameters, including pathological T staging and N staging, which are predictors of poor prognosis (Meng et al, 2015).

Liver Cancer

NDC80 expression has been analyzed by RT-PCR in 42 paired hepatocellular carcinoma (HCC) and adjacent tissues. The study has revealed that NDC80 levels are significantly higher in HCC cells as compared with adjacent tissues (Ju et al, 2017). A gene expression profile dataset of 10 HCC and 10 control samples analysed for gene ontology has identified NDC80 as member of a group of cell division-related genes that are up-regulated in HCC. Moreover, Ndc80 has been identified as an "hub" protein in HCC cancer, as revealed by protein-protein interaction network construction and module detection using the STRING online tool (Yan et al, 2017).

Gastric Cancer

mRNA overexpression of the four genes comprising the Ndc80 complex has been observed in primary resected gastric cancers when compared with the corresponding normal mucosae (Kaneko et al, 2009). More recently, RT-PCR and immunohistochemical staining of 42 gastric cancer and paired non-cancer tissues showed higher expression of both Hec1 mRNA and protein in gastric cancers as compared with non-tumor tissues. Hec1 staining was observed in 90% of cancer samples whereas positive staining was rarely observed in non cancer tissues. Positive staining of Hec1 was also observed in dysplasia glands, a precancerous lesion, suggesting an important role of Hec1 in the early stage of gastric tumorigenesis (Qu et al, 2014).

Prostate Cancer

Hec1 mRNA overexpression has been detected in human Prostate Cancer (PCa) tissues and higher mRNA and protein levels have been found in several PCa cell lines (Wang et al, 2015). The same study has also identified a long-non-coding RNA (LncRNA BX647187) as up-regulated in human PCa tissues and cell lines. The study also showed that LncRNA levels are positively regulated by Hec1, as they were strongly reduced upon Hec1 depletion. Interestingly, suppression of BX647187 significantly reduced cell proliferation and promoted apoptosis of PCa cells (Wang et al, 2015).

Colon cancer

Overexpression of Ndc80 mRNA has been reported in colorectal cancer tissues (Kaneko et al, 2009; Miyata et al, 2015). High levels of Ndc80 protein have been also observed in several colon cancer cell lines (Xing et al, 2016). Immunohistochemical analysis on tissue samples demonstrated that the rate of Ndc80-positive cells was significantly higher in colon cancer specimens than in normal colon tissues. Faster cell proliferation and greater migration ability was observed in colorectal SW480 cells transfected with an Ndc80-expressing vector as compared to controls (Xing et al, 2016).

Oligodendrogliomas

A study of microarray and RNA sequencing on normal brain tissue as compared to grade II and III oligodendrogliomas (ODs) has identified a co-expression network of six mitosis-regulating genes (NDC80 is among these) associated with malignant progression and prognosis in ODs. Validation by quantitative PCR of the six gene network has been obtained in a second group of ODs patients. (Liu et al, 2015).

Lung Cancer

Co-overexpression of Nuf2 and Ncd80, members of the evolutionarily conserved centromere protein complex (Ndc80), has been found in non-small cell lung carcinomas (NSCLC) and NSCLC cell lines (Hayama et al, 2006). Immunohistochemical analysis using lung cancer tissue microarray confirmed high levels of the two proteins in the great majority of lung cancers of various histological types (Hayama et al, 2006). The same study demonstrated that NSCLC patients with abundant expression of Nuf2/Ndc80 experience a shorter tumor-specific survival period (Hayama et al, 2006).

Ovarian Cancer

A RNA interference lethality screen of the human druggable genome has identified NDC80 among the four genes with a role in growth or survival of ovarian cancer cell lines. The study demonstrated that ovarian tumorigenic cells are comparatively more vulnerable to Ndc80 down-regulation compared with non-tumorigenic cells. Finally, Ndc80 was found overexpressed in nearly 100% of the samples in two independent cohorts of patient samples (Sethi et al, 2012).

Endometrial Cancer

A study of cDNA microarray has identified NDC80 as an up-regulated gene in serous endometrial adenocarcinomas. NDC80 was found to be member of a cluster of 46 genes exhibiting >2-fold differences in expression between serous endometrial adenocarcinomas and endometrioidones. Quantitative PCR and immunohistochemistry for Ndc80 confirmed the array results. Using unsupervised and supervised

statistical analyses, this gene cluster has been demonstrated to statistically differentiate the two types of adenocarcinomas (Chen et al, 2011).

To be noted

Note

Aneuploidy and chromosome instability are strongly involved in tumorigenesis. It has been demonstrated that aneuploidy may also act as a tumor suppressive mechanism, depending on the tissue analyzed and its intrinsic chromosome instability (Weaver et al. 2007; Janssen and Medema 2013).

Since the crucial role of Hec1 in chromosome segregation, it represents a promising molecular target for developing new therapeutic approaches and molecules that exert their anticancer property by producing massive aneuploidy and cell death in cancer cells. Concordantly, expression of a Hec1 protein modified at its N-terminus, the region of interaction with microtubules, has been shown to massively kill cancer cells both in vitro and in tumor xenografts (Orticello et al, 2014; Mattiuzzo et al, 2011).

Several RNAi studies have provided direct demonstration of the anti-proliferative effects of Hec1 inactivation in cancer cell lines from different tumor types such as mesothelioma (Linton et al, 2014), NSCLC (Hayama et al, 2006), prostate (Wang et al, 2015), gastric (Qu et al, 2014), hepatocellular (Ju et al., 2015) or pancreatic cancer (Meng et al, 2015). Hec1 depletion by RNAi has also been found to inhibit tumor growth in mouse xenografts (Gurzov & Izquierdo, 2006; Li et al, 2007).

In the recent years, several approaches have been undertaken to target Hec1 by inhibitory small molecules. Given the role of the NEK2A-dependent phosphorylation of Hec1 in the SAC, small molecules capable of disturbing NEK2A-Hec1 interaction have been identified and optimized by different groups (Wu et al, 2008; Lee et al, 2014; Huang et al, 2014a). In a different approach, a virtual screening for small molecules able to bind at the Hec1-microtubule interaction surface has been undertaken (Ferrara et al, 2017). This study identified a small molecule that produces chromosome segregation defects in cancer cells and promotes cancer cell death through mitotic catastrophe (Ferrara et al, 2017) In both approaches, the identified small molecules significantly reduced tumor growth in xenograft models (Huang et al, 2014b; Wu et al, 2008; Ferrara et al, 2017).

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